

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-264

CHEMISTRY REVIEW(S)

NDA 22-264

INVEGA® SUSTENNA
(paliperidone palmitate extended release injectable suspension)

Janssen Pharmaceutica N.V.

Review #2

David J. Claffey, Ph.D.
ONDQA

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Chemistry Review Data Sheet

1. NDA 22-264
2. REVIEW #:2
3. REVIEW DATE: 20 JUL 2009
4. REVIEWER: David J. Claffey, PhD

5. PREVIOUS DOCUMENTS:

Previous Documents

IND 67,356
Original NDA
Amendment (BC)
Amendment (BC)
Amendment (BL)
Amendment (BC)

Document Date

6 MAY 2003
26 OCT 2007
26 MAY 2008
13 JUN 2008
2 JUL 2008
11 JUL 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed

Amendment N-0026

Amendment N-0028
Amendment N-0033
Amendment N-0038
Amendment N-0039
Amendment N-0040
Amendment N-0041

Document Date

3 FEB 2009

24 FEB 2009
22 MAY 2009
16 JUL 2009
17 JUL 2009
20 JUL 2009
20 JUL 2009

Chemistry Review Data Sheet

7. NAME & ADDRESS OF APPLICANT:

Janssen, L.P.
Name: Johnson & Johnson Pharmaceutical Research &
Development, LLC
Office 12607, 1125 Trenton-Harbourton Road,
Address: Titusville, NJ 08560

Representative: Kelly Ward (for CMC related issues)

Telephone: 609-730-2056

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: **INVEGA® SUSTENNA**
- b) Non-Proprietary Name (USAN): Paliperidone palmitate
- c) Code Name/# (ONDC only): JNJ16977831; R092670
- d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antipsychotic

11. DOSAGE FORM: extended release injectable suspension

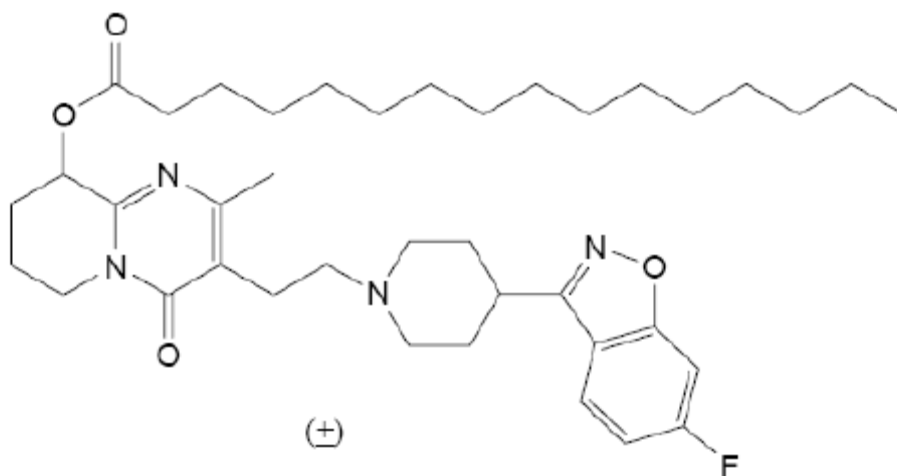
12. STRENGTH/POTENCY: 39 mg, 78 mg, 117 mg, 156 and 234 mg of
paliperidone palmitate (data for (b) (4) strength was provided but applicant is not
seeking approval for this strength at this time).

13. ROUTE OF ADMINISTRATION: Intramuscular

Chemistry Review Data Sheet

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)☐ SPOTS product – Form Completed☒ Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

(9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoateEmpirical formula: C₃₉H₅₇FN₄O₄

Molecular weight: 664.89

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
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Chemistry Review Data Sheet

20902	II	Janssen Pharmaceutic a, N.V.	Paliperidone palmitate as manufactured in Beerse and Cork, Ireland Belgium	1	Adequate	07/18/2008	T. Ocheltree David Claffey
18915	II	Janssen Pharmaceutic a, N.V.	Paliperidone (R076477 "crude") as manufactured in Beerse, Belgium	1	Adequate	07/14/2008	T. Ocheltree
(b) (4)	III	(b) (4)		1	Adequate		David Claffey
	III			1	Adequate	07/14/2008	By T. Ocheltree
	III			3	Adequate	06/25/2008	By Y. Sun
	III			1	Adequate	06/03/2008	By J. Metcalfe

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: N/A

Chemistry Review Data Sheet

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics			
EES	Acceptable Acceptable	15 APR 2008 2 JUL 2009	Shawnte Adams E Johnson
Pharm/Tox	Approval recommendation	17 JUN 2009	Elzbieta Chalecka-Franaszek
Biopharm	acceptable	01-AUG-2008	John Duan
LNC	Provided recommendation		Refer to review
CDRH	Acceptable	6 MAY 2009	William Burdick
Microbiology	Approval recommendation	30 JUN 2008 4 May 2009 (Cork Site)	John Metcalf

The Chemistry Review for NDA 22-264

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Recommend approval from a CMC perspective.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

On 20 JUL 2009 (N-0041) the applicant committed to adding “a clearly visible fill line to the syringe so that the health care provider can ensure that the syringes contain the required volume of suspension prior to administration and that no gross leakage or evaporation of the syringe contents has occurred during storage or shipping”.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Paliperidone is a selective, monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D₂) and serotonin (5-hydroxytryptamine [5-HT]) type 2A (5HT_{2A}) antagonism of the newer second generation, antipsychotic drugs.

Drug Product

Paliperidone palmitate suspension for injection (F013) was developed as a monthly intramuscular injectable suspension for the treatment of schizophrenia. Each milliliter of paliperidone palmitate (156 mg/mL) is equivalent to 100 mg/mL of paliperidone. The drug product was developed in six dosage strengths: 39 mg, 78 mg, 117 mg, 156 mg, (b) (4) and 234 mg of paliperidone palmitate (equivalent to 25 mg, 50 mg, 75 mg, 100 mg, (b) (4) and 150 mg of paliperidone, respectively). This application proposes the marketing of all (b) (4) strength. The drug product is packaged in (b) (4) transparent cyclic olefin copolymer (COC) syringes and marketed as kit containing two needles for administration (a 22-g, 1½-inch safety needle and a 23-g, 1-inch safety needle). (b) (4)

The extremely low solubility of paliperidone palmitate allows the formulation of an extended release product where the isotonic aqueous buffer solvent penetrates the muscle tissue and the undissolved paliperidone palmitate particles are localized at the site as a poorly soluble agglomerate. Paliperidone palmitate is stated to dissolve slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation.

Stability data provided in the previous review cycle support a 24 month expiry period.

Executive Summary Section

Drug Substance

Paliperidone palmitate (R092670 drug substance) is the palmitate ester of paliperidone (R076477), the major active metabolite of risperidone. It is practically insoluble in aqueous media over a broad pH range. This low solubility allows the drug substance to be formulated as a suspension for intramuscular injection that provides an extended release profile that is a function of drug substance particle size. The drug substance particle size is controlled by the (b) (4) executed during the drug product manufacturing process to (b) (4)

(b) (4) have been demonstrated to not impact drug product performance. All drug substance physiochemical information and manufacturing process information is referenced to DMF 20902.

Summary of CMC related review issues addressed in the course of this review cycle:**Complete response issues:**

CR #1: DMF (b) (4) for (b) (4) previously found deficient. Holder resolved these deficiencies to the satisfaction of the CDRH reviewer. It should be noted that the applicant committed to adding a fill line to the syringe barrel within 12 months of approval of this application (N-0041).

CR #2: Strength needs to match the established name: The Division determined in consultation with the CDER Labeling and Nomenclature Committee and DMEPA that the strengths should be expressed in terms of the paliperidone palmitate rather than paliperidone. The applicant agreed to this change (labeling received 16 JUL 2009). Although many examples exist in approved products of name-strength mismatches and of the incomplete name of an ester being part of the established name, this decision is part of the current Agency policy to implement a uniform and consistent policy on this matter.

CR#3: Genotoxic impurities issue: This issue was resolved by re-evaluation of the data by this reviewer and through the applicant agreeing to add a test for (b) (4) to the drug substance specification with a combined limit of (b) (4) ppm.

CR#4: Addition of a specification for (b) (4) to the drug product specification. This issue was resolved by the applicants demonstration that their addition of citric acid (b) (4) through the expiry period.

CR#5: The syringe barrel should contain calibrated markings to indicate the appropriate volume of the drug product in the syringe and allow for partial doses to be given from the syringe: this issue was resolved when the division agreed in the 28 NOV 2008 meeting that calibration markings would not be necessary (see meeting notes). A more detailed response regarding the addition of a fill line on the syringe barrel was provided in the 22

Executive Summary Section

MAY 2009 amendment (detailed response to IR#6 and summary of fill line issue on next page).

CR#6: A transparent label that allows for the viewing of the syringe calibration marks and drug product should be used for labeling of the syringes. As was agreed upon in response to CR#5, the calibrated markings would not be required, but the Agency requested that a fill line be added to the syringe barrels within 12 months of marketing approval. The applicant committed to doing so (email 16 JUL 2009, amendment N-0041).

Other CMC-related issues encountered during this review cycle:

- **Summary of genotoxin control issue:** The CR letter included a request by the previous CMC reviewer (Dr. Terrence Ocheltree) to limit the levels of known genotoxins (b) (4) and (b) (4) to a level of (b) (4) ppm. This corresponded to a maximum daily exposure of (b) (4). During the course of this review cycle the applicant proposed amending the application with an additional 150 mg strength – therefore the recommended limit for genotoxins was lowered to (b) (4) ppm so that the maximum patient daily exposure would remain at the (b) (4). The applicant proposed carrying out testing for genotoxin (b) (4) in the first ten commercial scale drug substance batches of intermediate ‘crude’ drug substance then deleting this test if levels remained at acceptable levels. The applicant describes their “science-based” “criticality analysis” approach to determine critical steps and controls for drug substance manufacturing. This criticality analysis was supported by a “detailed knowledge of the origin and fate of impurities, including potentially genotoxic impurities”. However this ‘detailed knowledge’ apparently did not include consideration of the (b) (4) of (b) (4) until the question was raised by the Agency in the 24 APR 2009 information request. One would assume that this should have been part of the most basic ‘criticality analysis’. The data provided did generally demonstrate that the synthetic process is capable of reducing levels of some or all of the genotoxin at laboratory and pilot scale. Three lots at commercial scale also showed levels of (b) (4) ppm of genotoxins. Although the latter are the most convincing data, it was in this reviewer’s evaluation that the experience to date remains limited and does not account for typical variations in the manufacturing environment (e.g. personnel and process variability). Further, the risk associated with these impurities is high as the harm that they have the potential to cause is both high and not immediately detectable by the patients. The burden on the applicant to test for these known genotoxins does not appear to be high relative to this risk. In this reviewer’s re-evaluation of the applicants responses and taking into consideration the synthetic process and the likely fate of (b) (4) and (b) (4) we requested that the applicant control (at drug substance release) (b) (4) and its (b) (4) to a combined level of (b) (4) ppm. The applicant accepted this recommendation in the 16 JUL 2009 amendment (N-0038).
- **Dosage form designation issue:** the applicant proposed using (b) (4) as the dosage form designation in the established name. This is in line with the other approved drug in this class of anti-psychotic depots – Risperdal Consta (risperidone) (b) (4)

Executive Summary Section

(b) (4) However in the Agency's attempt to implement a more uniform and consistent policy in this matter, the Labeling and Nomenclature Committee recommended that the dosage form designation 'extended-release injectable suspension' be used. "Injectable Suspension" is one of five acceptable dosage form designations listed in USP <1> and "extended release" is the only available modifier to indicate its prolonged release in the CDER Data Standard Manual (DSM). This recommendation was conveyed to the applicant during labeling negotiations. The applicant proposed the use of (b) (4) as there was no precedent in USP or DSM to use "extended release injectable suspension". Further, they raised the possibility that if "extended release" were used that confusion would exist with the marketed INVEGA (paliperidone) extended-release tablets. The Agency acknowledged that "extended-release injectable suspension" is not mentioned in USP - as a monograph has not yet been produced for the single marketed product that uses this dosage form designation i.e. Vivitrol (naltrexone for extended release injectable suspension). In an attempt to differentiate the two "paliperidone" containing extended-release products, modifications of the proprietary name or the carton labels will be carried out in consultation with DMEPA (internal meeting 20 JUL 2009). The applicant accepted the use of the recommended dosage form designation (telcon 17 JUL 2009).

- (b) (4)

- **Syringe Fill line issue:** The applicant was asked to add a fill line to the syringe barrels.

(b) (4)

However these controls are not capable of detecting vials that leak after product release, either through a defect in the syringe, the plunger or the stopper. Such gross leaks may be detectable by the health care provider as the presence of white precipitate should be obvious. However, small leaks that result in leakage and/or evaporation of the water within the suspending medium would not be readily detected by the health care provider if a fill line were not present and the vial contents not visible. Further, such leaks could also result in microbial contamination of the drug product. It

Executive Summary Section

should be stressed that data from batch release and stability studies provide no evidence that such leaks will routinely occur, however the risk to the patient is high as the detectability of such faults is low and severity of harm is high when one considers the indication and the relatively long period between treatments. It should be stressed that there are no known unique quality defects associated with this product above and beyond that of, for example, a typical tablet dosage form. Even in a six sigma process several defects per million are allowable, however, the end user generally has the opportunity to reduce this risk of quality defects further if a tablet appears cracked, speckled, or off-color. A clearly visible fill line will offer the end user of this product that same opportunity.

It should be noted that in this reviewers non-exhaustive search of approved prefilled syringe products, all possessed either a fill line or graduations. Most products contained instructions for the health care provider to check that the level of liquid in the syringe is at or close to a fill line, or that it should be between two fill lines. Prefilled syringes are likely to occupy an increasing share of the US parenteral dosage form market due to their convenience, less waste of drug substance involved and technology-driven reductions in the cost of their production. Should this product have been approved as the applicant proposed, it would appear to be the first approved prefilled syringe without a fill line. Considering the nature of the proposed indication and the relatively lengthy time between administrations this reviewer does not consider the justifications provided for the absence of a fill line to be sufficient to set such a precedent. On 20 JUL 2009 (N-0041) the applicant committed to adding “a clearly visible fill line to the syringe so that the health care provider can ensure that the syringes contain the required volume of suspension prior to administration and that no gross leakage or evaporation of the syringe contents has occurred during storage or shipping”.

- The applicant amended DMF 20902 to include the Cork site as a manufacturing site for “sterile grade” drug substance. Previously the Cork site manufactured the intermediate “crude” grade drug substance. This amendment was found to be acceptable by this reviewer. The Office of Compliance issued an ‘acceptable’ recommendation on 2 JUL 2009.
- Proposed marketing of the 234 mg dosage strength. This was found acceptable from a CMC perspective.
- Clarification of accepted dissolution acceptance criteria: The CR letter contained the biopharm reviewer’s request that the applicant accept a version of the dissolution specification that lacked the initial 1.5 minute time point. This time point appeared to have been omitted as it was not part of the IVIVC as evaluated by the biopharm reviewer, but was a quality control to protect against ‘dose dumping’. The applicant agreed to accept this incomplete dissolution specification as part of their complete response. Clarification was sought from the applicant on this issue. They stated (telecon with PMQ Don Henry 14 JUL 2009) that the 1.5 minute time point was still in place and that the drug product specifications are unchanged from those proposed in the initial submission

Executive Summary Section

(Attachment 2 of this review). This adequately resolves this issue. We recommend that the following complete dissolution method be included in the action letter:

Parameter	Dissolution Method and Specifications	
Apparatus type:	USP Type II (paddle)	
Media:	0.001 M HCl containing 0.489% Polysorbate 20 (Tween®20)	
Volume:	900 ml	
Temperature:	25 ± 0.5 °C	
Frequency:	50 rpm	
Sampling Times:	1.5, 8, 20, and 45 minutes	
Acceptance	1.5 minutes	NMT ^{(b) (4)} % of Label Claim
Criteria:	8 minutes	^{(b) (4)} of Label Claim
	20 minutes	^{(b) (4)} of Label Claim
	45 minutes	^{(b) (4)} of Label Claim
Analysis	HPLC UV detection	

B. Description of How the Drug Product is Intended to be Used

Treatment is initiated with a dose of 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle. The recommended monthly maintenance dose is 117 mg; some patients may benefit from lower or higher maintenance doses within the recommended range of 39 mg to 234 mg based on individual patient tolerability and/or efficacy. Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

The product is administered by intramuscular injection. For deltoid injection, a 1 ½-inch 22G needle is recommended for patients ≥ 90 kg (≥ 200 lb) or a 1-inch 23G needle is recommended for patients < 90 kg (< 200 lb). For gluteal injection, a 1 ½-inch 22G needle is recommended regardless of patient weight.

C. Basis for Approvability or Not-Approval Recommendation

All outstanding CMC related issues contained in the CR letter and the information requests of 24 APR 2009 and 8 JUL 2009 have been resolved. DMF 20902 for the drug substance manufacture and DMF ^{(b) (4)} for the ^{(b) (4)} were found to be acceptable. The applicant accepted the proposed changes to the established name, labeled strengths and the control of genotoxic impurities. The Office of Compliance issued an acceptable recommendation on 2 JUL 2009. On 20 JUL 2009 (N-0041) the applicant agreed with the Agency recommendation to add “a clearly visible fill line to the syringe so that the health care provider can ensure that the syringes contain the required volume of suspension prior to administration and that no gross leakage or evaporation of the syringe contents has occurred during storage or shipping”.

Executive Summary Section

III. Administrative**A. Reviewer's Signature****B. Endorsement Block**

ChemistName/Date: Same date as draft review

ChemistryTeamLeaderName/Date

ProjectManagerName/Date

C. CC Block

41 pp withheld immediately following this page as (b)(4) CCI/TS.



**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

David Claffey
7/22/2009 10:18:28 AM
CHEMIST

Thomas Oliver
7/22/2009 11:05:08 AM
CHEMIST

NDA 22-264

INVEGA® SUSTENNA (paliperidone palmitate) Injection

Janssen Pharmaceutica N.V.

Terrance Ocheltree, R.Ph., Ph.D.

Office of New Drug Quality Assessment

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Chemistry Review Data Sheet

1. NDA 22-264
2. REVIEW #1
3. REVIEW DATE: 10-AUG-2008
4. REVIEWERS: Terrance Ocheltree, R.Ph., Ph.D.
5. PREVIOUS DOCUMENTS:

Previous Documents
IND 67356

Document Date
05/06/2003

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed
Original (CMC)
Amendment (BC)
Amendment (BC)
Amendment (BL)
Amendment (BC)

Document Date
10/26/2007
05/29/2008
06/13/2008
07/02/2008
07/11/2008

7. NAME & ADDRESS OF APPLICANT:

Name: Janssen, L.P.
Johnson & Johnson Pharmaceutical Research &
Development, LLC
Address: Office 12607, 1125 Trenton-Harbourton Road,
Titusville, NJ 08560
Kelly Ward (for CMC related issues)
Representative: Cross-Pharma CMC Regulatory Affairs
e-mail: kward1@prdus.jnj.com
Telephone: 609-730-2056 (phone)
609-730-2706 (fax)

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: **INVEGA® SUSTENNA**

Non-Proprietary Name (USAN): Paliperidone palmitate

Code Name/# (ONDC only): JNJ16977831; R092670

b) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Antipsychotic

11. DOSAGE FORM: Suspension for Injection

12. STRENGTH/POTENCY: 39 mg, 78 mg, 117 mg, and 156 mg of paliperidone palmitate, equivalent to 25 mg, 50 mg, 75 mg, and 100 mg of paliperidone, respectively

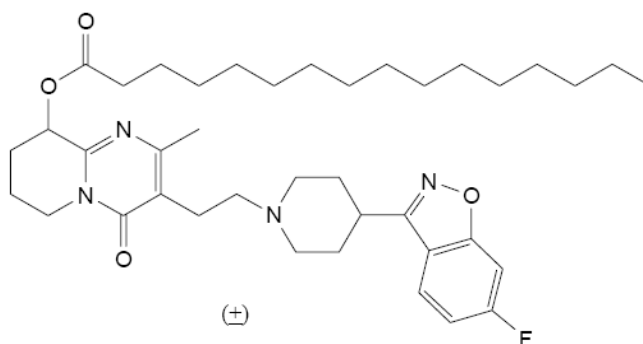
13. ROUTE OF ADMINISTRATION: Intramuscular injection

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):☐ SPOTS product – Form Completed☒ Not a SPOTS product

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(9*RS*)-3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidin-1-yl]ethyl]-2-methyl-4-oxo-6,7,8,9-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate
(±)-3-[2-[4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-9-yl hexadecanoate

Chemistry Review Data Sheet



The empirical formula is: $C_{39}H_{57}FN_4O_4$

The molecular weight is: 664.89

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
20902	II	Janssen Pharmaceutica, N.V.	Paliperidone palmitate as manufactured in Beerse, Belgium	1	Adequate	07/18/2008	By T. Ocheltree
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(b) (4)	III		(b) (4)	1	Inadequate	07/18/2008	By T. Ocheltree
	III			1	Adequate	07/14/2008	By T. Ocheltree
	III			3	Adequate	06/25/2008	By Y. Sun
	III			1	Adequate	06/03/2008	By J. Metcalfe

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

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3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

Chemistry Review Data Sheet

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/ REVIEWER	COMMENTS
Biometrics	N/A			No statistical analysis of drug product stability data deemed necessary.
EES	Site inspections	15-APR-2008	Acceptable	
Pharm/Tox	N/A			
Biopharm	IVIVC	01-AUG-2008	Approval	The IVIVC model is established.
ODS/DMETS	Labeling consult		Pending	
Methods Validation	N/A			
EA	N/A			Applicant cites 21 CFR 25.31(b) as applicable.
CDRH	Syringe assembly		Inadequate/W. Burdick	Inadequate, pending response to comments
Microbiology	(b) (4)		Approval/J. Metcalf	

The Chemistry Review for NDA 22-234

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is recommended for **approvable** with respect to the chemistry, manufacturing, and controls (CMC). The sites recommendation from the Office of Compliance is acceptable. The applicant and the Holder of the Type II Drug Master File (DMF) referenced in the NDA still need to adequately respond to a number of CMC issues outlined in either this review or the review for DMF

(b) (4)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Paliperidone is a selective, monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D₂) and serotonin (5-hydroxytryptamine [5-HT]) type 2A (5HT_{2A}) antagonism of the newer, second generation, antipsychotic drugs.

Drug Product

Paliperidone palmitate suspension for injection (F013) was developed as a monthly intramuscular injection for the treatment of schizophrenia. Each milliliter of paliperidone palmitate (156 mg/mL) is equivalent to 100 mg/mL of paliperidone. The drug product is developed in (b) (4) dosage strengths: 39 mg, 78 mg, 117 mg, 156 mg, (b) (4) and 234 mg of paliperidone palmitate, equivalent to 25 mg, 50 mg, 75 mg, 100 mg, (b) (4), and 150 mg of paliperidone, respectively. However, it will only be marketed in the 39 mg, 78 mg, 117 mg, and 156 mg strengths. The drug product is packaged in (b) (4) transparent cyclic olefin copolymer (COC) syringes and marketed as either a retail kit (b) (4) (b) (4) the retail kits contains 2 needles for administration (a 22-g, 1½-inch safety needle and a 23-g, 1-inch safety needle) (b) (4)

The extremely low solubility of paliperidone palmitate allows the formulation of a long-acting product where the isotonic aqueous buffer solvent penetrates the muscle tissue and the undissolved paliperidone palmitate particles are localized at the site as agglomerate. Due to extremely low water solubility, paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation.

Executive Summary Section

Drug Substance

Paliperidone palmitate (R092670 drug substance) is the palmitate ester of paliperidone (R076477), the major active metabolite of risperidone. It is practically insoluble in aqueous media over a broad pH range. This low solubility allows the drug substance to be formulated as a suspension for intramuscular injection that provides an extended release profile that is a function of drug substance particle size. The drug substance particle size is controlled by the (b) (4) executed during the drug product manufacturing process to (b) (4)

have been demonstrated to not impact drug product performance.

All drug substance physiochemical information and manufacturing process information is referenced to DMF 20,902.

B. Description of How the Drug Product is Intended to be Used

Paliperidone palmitate suspension for injection (F013) was developed in (b) (4) dosage strengths (but will only be marketed in the 39 mg, 78 mg, 117 mg, and 156 mg strengths) as a once monthly intramuscular injection for the treatment of schizophrenia. The long acting injectable form is reported to offer advantages over the currently available dosage forms to facilitating patient compliance and assurance that the drug is delivered.

C. Basis for Approvability or Not-Approval Recommendation

The recommendation of Approvable for NDA 22-264 is based the requirement that the applicant adequately responding to numerous outstanding CMC information requests. The following comments have been sent, but not responded to at the time of this review:

1. The Drug Master File (b) (4) for (b) (4) has been found to be inadequate to support the NDA. Letters detailing the deficiencies have been issued to the designated agents.
2. The term (b) (4) is not a recognized dosage form according to the CDER Data Standards Manual and therefore should not be used in the labeling of your drug product.
3. It is FDA policy that the strength of the drug substance has to be provided as part of the established name. The proposal to just remove the reference to strength (mg) from the product name is not sufficient. The historical evidence provided to justify your proposal is not sufficient because most products listed were approved quite awhile ago and do not reflect current practices. According to information you provided in the original NDA submission “paliperidone palmitate dissolves slowly after intramuscular injection before being hydrolyzed to paliperidone and absorbed into the systemic circulation”, which indicates that paliperidone palmitate is a prodrug and that the palmitate ester exerts a biopharmaceutic effect.

Executive Summary Section

4. [REDACTED] (b) (4)
5. Establish an acceptance criteria equal to or less than (b) (4) ppm for the two genotoxic impurities, (b) (4) and (b) (4)

The following comments have not been sent to the applicant and should be included in the action letter:

6. Include a test and an acceptance limit for [REDACTED] (b) (4) in the drug product specification.
7. The syringe barrel should contain calibrated markings to indicate the appropriate volume of drug product in the syringe and allow for partial doses to be given from the syringe.
8. A transparent label that allows for the viewing of the syringe calibration marks and drug product should be used for labeling of the syringes.
9. Replace the term [REDACTED] (b) (4) in the established name of the product with "Extended Release Suspension for Injection" to appropriately reflect the proposed dosage form.

III. Administrative

This NDA was submitted electronically as a 505(b)(1) application. A Quality Overall Summary is included in the application.

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

T.Ocheltree/ONDQA/Reviewer
R. Sood/ONDQA/Branch Chief

C. CC Block

S.Goldie/ONDQA/Regulatory PM
K.Updegraff/DPP/Regulatory PM
T.Oliver/ONDQA/PAL

60 pages withheld immediately following this pages as (b)(4) CCI/TS.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Terrance Ocheltree
8/15/2008 05:45:01 PM
CHEMIST

Ramesh Sood
8/15/2008 05:46:25 PM
CHEMIST